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(54) Pharmaceutical compositions for topical use on the basis of ketoprofen

Pharmazeutische Zusammensetzungen zum topischen Gebrauch enthaltend Ketoprofen
Compositions pharmaceutiques à usage topique contenant du kétoprofène

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(74) Representative: Klausner, Erich
c/o Ufficio Internazionale Brevetti
Ing. C. Gregorj S.p.A.
Via Dogana 1
20123 Milano (IT)

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• PATENT ABSTRACTS OF JAPAN vol. 016, no.
093 (C-0917), 6 March 1992 -& JP 03 275619 A
(NISSUI SEIYAKU KK), 6 December 1991 -&
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(NISSUI SEIYAKU KK)

(73) Proprietor: Bayer S.p.A.
20156 Milano (IT)

(72) Inventor: Dondi, Gilberto
Cusano Milanino (MI) (IT)

EP 0 756 870 B1

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Description

[0001] The topical treatment of rheumatic diseases or traumatic affections is often carried out using topical pharmaceutical formulations such as plasters, ointments, creams, gels, sprays and the like.

5 [0002] The aim of the topical treatment is to establish an analgesic and/or therapeutic effect.

[0003] The therapeutic effect is established depending on the penetration ability of the drug in the area suffering from the existing pathology.

10 [0004] It is generally accepted that the penetration route of a substance inside and through the skin is the skin itself and not other structures such as hair follicles or sudoriferous glands, although these may represent concomitant penetration routes.

15 [0005] There are well-founded reasons to believe that such structures do not constitute the prevalent routes; in humans, for example, palmar or plantar regions are provided with sudoriferous glands in an amount which is three times higher than in the other body regions; however, these regions are less capable of absorbing penetrating substances. Now, therefore, the prevailing opinion among the skilled in the art is that the transport of molecules of pharmacologically active substances occurs through passive diffusion and is strongly affected positively by skin hydration. Ointments which leave an occlusive film on the cutaneous surface produce hydration because of sweat accumulation at the skin-ointment interface and consequently they promote penetration.

20 [0006] Among the other factors affecting the absorption is heat because it promotes a state of hyperthermia. Cold acts in the opposite way because it slows down the capillary circulation.

[0007] Among the many preparations available there are two types of spray formulations:

- compositions with a cooling effect which basically favors the analgesic action of the composition
- compositions with a revulsive/rubefacient effect which facilitates the blood supply with a consequent sensation of wellbeing.

25 [0008] US-A-4704406 refers to a sprayable preparation of ketoprofen, suitable for topical application, containing as solvent a mixture of one or more volatile solvents such as ethanol, propanol or isopropanol and one or more non volatile solvents such as propylene glycol, glycerin, a liquid polyethylene glycol or a polioxyalkylene glycol, in the weight ratio range of 1:1 to 20:1.

30 [0009] JP-A-3275619 refers to a topical composition containing a medicament, inter alia ketoprofen, a water-insoluble macromolecule, preferably a cellulose derivative, a plasticiser such as glycerol, glycerol ester, propylene glycol, polyethylene glycol, dimethyl (or diethyl) terephthalate, an organic solvent such as ethanol or propanol.

[0010] Recently, attempts have been made to use pharmacologically active substances generally employed parenterally and/or enterally. As a consequence, however, the need arose for agents capable of promoting the drug penetration through the skin.

35 [0011] In this connection, a number of different substances have been suggested such as alcohols, polyglycols, surfactants of different structures, without a common or clearly demonstrable result.

[0012] The more efficient system in order to assure the effectiveness of the pharmaceutical composition must be based on two types of action:

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- a greater blood supply with an increase in skin permeability,
- a better penetration due to the presence of suitable selected agents.

The present invention refers to a pharmaceutical spray composition, for topical use, on the basis of ketoprofen, characterized in that it has the following percent composition, by weight:

ketoprofen	2 to 10
alcohol	40 to 80
propylene glycol	5 to 10
poloxamer or polyoxyethylated castor oil	1 to 10
polyvinylpyrrolidone	2 to 10
ethanolamine	0.9 to 4.4
water	q.s. to 100

55 [0013] In particular, a sprayable pharmaceutical formulation, comprising an antirheumatic/analgesic active substance, such as ketoprofen, was developed, which formulation has the following percent composition (weight/weight):

ketoprofen	2-10
isopropyl alcohol	40-80
benzyl nicotinate	0.2-2
propylene glycol	5-10
poloxamer	1-10
polyvinylpyrrolidone	2-10
ethanolamine	0.9-4.4
water	q.s. to 100

[0014] In the above-mentioned formulation, benzyl nicotinate is the rubefacient agent which, as it is known to the skilled in the art, can be substituted with other substances such as, e.g., camphor, menthol, capsicum, or mixtures thereof; propylene glycol and isopropyl alcohol, or other alcohols commonly used in art of drugs for topical use, are the principal carriers, poloxamer (ethylene-polyoxypropylene block copolymer), which may be substituted by an equal amount of polyoxethylated castor oil, acting as a penetration agent, and polyvinylpyrrolidone is added as a film forming agent in order to confer adhesive properties to the skin and to favor the absorption of the topical composition of the present invention.

[0015] A critical parameter of the present formulation is the pH value of the ketoprofen solution in the hydroalcoholic carrier in order to give stability to the pharmaceutical composition. The best results were obtained for pH values between 5 and 7. According to the present invention these values can be obtained by adding suitable neutralizing agents such as, e.g. ethanolamine, lysine, triethanolamine, methylglucamine and, generally, any suitable amine of the kind used for the manufacture of pharmaceutical compositions.

[0016] The manufacture of ketoprofen spray solutions is carried out by dissolving the ingredients in a previously prepared alcohol-water mixture. Finally, ethanolamine is added and the obtained pH value is checked and adjusted, if necessary.

[0017] Then the composition is filled up in glass or pharmacologically inert plastic bottles, such as, e.g., opaque, white polyethylene, equipped with a mechanical pump for spraying pharmaceutical compositions for topical use in an exactly dosed amount.

[0018] The present invention is better illustrated by the following examples. A person skilled in the art of pharmaceutical compositions will, without any difficulty, be able to adapt the process parameters to the particular needs without, thereby, departing from the gist of the invention.

Example 1

[0019] To a solution of:

isopropyl alcohol	69.5 g
purified water	10.0 g

the following ingredients are added under stirring:

poloxamer 407	2.0 g
menthol	0.2 g
propylene glycol	8.0 g
benzyl nicotinate	0.2 g
polyvinylpyrrolidone 25	4.0 g
ketoprofen	5.0 g

[0020] To the so obtained homogeneous mixture

ethanolamine	1.1 g
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is added; the final pH value of the preparation is 6.5.

[0021] Then the solution is divided and packed in dark glass or white polyethylene bottles, equipped with a mechanical sprayer.

Example 2

[0022] To a solution of:

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ethyl alcohol	66.9 g
purified water	7.0 g

the following ingredients are added, under stirring:

10

poloxamer 407	2.0 g
propylene glycol	10.0 g
benzyl nicotinate	2.0 g
polyvinylpyrrolidone 25	4.0 g
ketoprofen	5.0 g

15

[0023] To the so prepared mixture

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ethanolamine	1.1 g
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is added; the final pH value of the preparation is 6.5.

Example 3

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[0024] To a solution of:

30

ethyl alcohol	66.9 g
purified water	7.0 g

the following ingredients are added, under stirring:

35

polyoxyethylated castor oil	2.0 g
propylene glycol	10.0 g
benzyl nicotinate	2.0 g
polyvinylpyrrolidone 25	4.0 g
ketoprofen	5.0 g

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[0025] To the so prepared mixture

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ethanolamine	1.1 g
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is added; the final pH value of the preparation is 6.5.

Claims

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1. A pharmaceutical spray composition, for topical use, on the basis of ketoprofen, characterized in that it has the following percent composition, by weight:

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ketoprofen	2 to 10
alcohol	40 to 80
propylene glycol	5 to 10
poloxamer or polyoxyethylated castor oil	1 to 10
polyvinylpyrrolidone	2 to 10
ethanolamine	0.9 to 4.4

(continued)

water	q.s. to 100
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5 2. A pharmaceutical spray composition for topical use, according to claim 1, characterized in that its pH value is in
the range of from 5 and 7.

10 3. A pharmaceutical spray composition for topical use, according to claims 1 and 2, characterized by the following
percent composition, in parts by weight:

10	ketoprofen	5.0
	isopropyl alcohol	69.5
	purified water	10.0
15	poloxamer 407	2.0
	menthol	0.2
	propylene glycol	8.0
	benzyl nicotinate	0.2
20	polyvinylpyrrolidone 25	4.0
	ethanolamine	1.1

and a pH value of 6.5

25 4. A pharmaceutical spray composition, for topical use, according to claims 1 and 2, characterized by the following
percent composition, in parts by weight:

30	ketoprofen	5.0
	ethyl alcohol	68.9
	purified water	7.0
	poloxamer	2.0
35	propylene glycol	10.0
	benzyl nicotinate	2.0
	polyvinylpyrrolidone 25	4.0
	ethanolamine	5.0

and a pH value of 6.5

40 5. A process for manufacturing a pharmaceutical spray composition, for topical use, on the basis of ketoprofen according
to anyone of the preceding claims, characterized in that the ketoprofen is dissolved in a previously prepared
alcohol-purified water solution, followed by adding the other components of the composition, under continuous
stirring, adjusting the pH to a value in the range of 5 and 7, with a pharmaceutically acceptable amine neutralizing
agent.

45 Patentansprüche

50 1. Pharmazeutische Spray-Zusammensetzung für die topische Anwendung auf der Basis von Ketoprofen, dadurch
gekennzeichnet, dass sie die folgende Zusammensetzung in Gew.-% aufweist:

55	Ketoprofen	2 bis 10
	Alkohol	40 bis 80
	Propylenglykol	5 bis 10
	Poloxamer oder polyoxyethyliertes Kastoröl	1 bis 10
	Polyvinylpyrrolidon	2 bis 10
	Ethanolamin	0,9 bis 4,4

(fortgesetzt)

Wasser	q.s. auf 100
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5 2. Pharmazeutische Spray-Zusammensetzung für die topische Anwendung nach Anspruch 1, dadurch gekennzeichnet, dass ihr pH-Wert im Bereich von 5 bis 7 liegt.

3. Pharmazeutische Spray-Zusammensetzung für die topische Anwendung nach den Ansprüchen 1 und 2, dadurch gekennzeichnet, dass sie die folgende prozentuale Zusammensetzung in Gewichtsteilen aufweist;

10

Ketoprofen	5,0
Isopropylalkohol	69,5
gereinigtes Wasser	10,0
Poloxamer 407	2,0
Menthol	0,2
Propylenglykol	8,0
Benzylnikotinat	0,2
Polyvinylpyrrolidon 25	4,0
Ethanolamin	1,1
und ein pH-Wert von	6,5.

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4. Pharmazeutische Spray-Zusammensetzung zur topischen Anwendung nach Anspruch 1 und 2, dadurch gekennzeichnet, dass sie folgende prozentuale Zusammensetzung in Gewichtsteilen aufweist:

20

Ketoprofen	5,0
Ethylalkohol	68,9
gereinigtes Wasser	7,0
Poloxamer	2,0
Propylenglykol	10,0
Benzylnikotinat	2,0
Polyvinylpyrrolidon 25	4,0
Ethanolamin	5,0
und ein pH-Wert von	6,5.

25

5. Verfahren zur Herstellung einer pharmazeutischen Spray-Zusammensetzung zur topischen Anwendung auf der Basis von Ketoprofen nach irgend einem der vorhergehenden Ansprüche, dadurch gekennzeichnet, dass das Ketoprofen in einer zuvor hergestellten Alkohol/gereinigtem Wasser-Lösung gelöst wird, anschließend die anderen Komponenten der Zusammensetzung unter kontinuierlichem Röhren zugegeben werden, und der pH-Wert auf einen Wert im Bereich von 5 bis 7 mit einem pharmazeutisch verträglichen Amin-Neutralisierungsmittel eingestellt wird.

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Revendications

1. Composition pharmaceutique en spray à usage topique à base de kétoprofène, caractérisée en ce qu'elle présente la composition suivante exprimée en pourcentage en poids :

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Kétoprofène	de 2 à 10
Alcool	de 40 à 80
Propylèneglycol	de 5 à 10
Poloxamère ou huile de ricin polyoxyéthylée	de 1 à 10
Polyvinylpyrrolidone	de 2 à 10
Ethanolamine	de 0,9 à 4,4
Eau	autant que nécessaire jusqu'à la totalité

2. Composition pharmaceutique en spray à usage topique selon la revendication 1, caractérisée par ce que sa valeur de pH est comprise dans la plage allant de 5 à 7.

5 3. Composition pharmaceutique en spray à usage topique selon les revendications 1 et 2, caractérisée par la composition suivante exprimée en parties en pourcentage en poids :

10	Kétoprofène	5,0
	Alcool isopropylique	69,5
	Eau purifiée	10,0
	Poloxamère 407	2,0
	Menthol	0,2
	Propylèneglycol	8,0
15	Nicotinate de benzyle	0,2
	Polyvinylpyrrolidone 25	4,0
	Ethanalamine	1,1

et une valeur de pH de 6,5.

20 4. Composition pharmaceutique en spray à usage topique selon les revendications 1 et 2, caractérisée par la composition suivante exprimée en parties en pourcentage en poids :

25	Kétoprofène	5,0
	Alcool éthylique	68,9
	Eau purifiée	7,0
	Poloxamère	2,0
	Propylèneglycol	10,0
30	Nicotinate de benzyle	2,0
	Polyvinylpyrrolidone 25	4,0
	Ethanalamine	5,0

et une valeur de pH de 6,5.

35 5. Procédé de préparation d'une composition pharmaceutique en spray, à usage topique, à base de kétoprofène selon l'une quelconque des revendications précédentes, caractérisé en ce que le kétoprofène est dissous dans une solution préalablement préparée à base d'alcool et d'eau purifiée, suivi par l'ajout des autres composants de la composition, sous agitation continue, en ajustant le pH à une valeur comprise dans la plage allant de 5 à 7, avec un agent de neutralisation à base d'aminés pharmaceutiquement acceptable.

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(72) Inventor: Dondi, Gilberto
Cusano Milanino (MI) (IT)

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(74) Representative: Klausner, Erich
c/o Ufficio Internazionale Brevetti
Ing. C. Gregorj S.p.A.
Via Dogana 1
20123 Milano (IT)

(71) Applicant: Bayer S.p.A.
20156 Milano (IT)

(54) Pharmaceutical compositions for topical use on the basis of ketoprofen

(57) The invention relates to pharmaceutical spray compositions on the basis of ketoprofen, useful for the treatment of rheumatism and traumatic affections.

EP 0 756 870 A3



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EUROPEAN SEARCH REPORT

Application Number

DOCUMENTS CONSIDERED TO BE RELEVANT		
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim
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A	PATENT ABSTRACTS OF JAPAN vol. 016, no. 093 (C-0917), 6 March 1992 -& JP 03 275619 A (NITSUSUI SEIYAKU KK), 6 December 1991	1-5
A	* abstract * -& DATABASE WPI Section Ch, Week 9204 Derwent Publications Ltd., London, GB; Class A12, AN 92-028853 XP002093383 & JP 03 275619 A (NISSUI SEIYAKU KK) * abstract *	1-5
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		A61K
The present search report has been drawn up for all claims		
Place of search	Date of completion of the search	Examiner
THE HAGUE	15 February 1999	Boulois, D
CATEGORY OF CITED DOCUMENTS		
X: particularly relevant if taken alone	T: theory or principle underlying the invention	
Y: particularly relevant if combined with another	E: earlier patent document, but published on, or after the filing date	
document of the same category	D: document forming part of the application	
A: technological background	L: document cited for other reasons	
O: non-written disclosure		
P: intermediate document	S: member of the same patent family, corresponding document	

ANNEX TO THE EUROPEAN SEARCH REPORT
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This annex lists the patent family members relating to the patent documents cited in the above-mentioned European search report.
The members are as contained in the European Patent Office EDP file on
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